P1 1184276

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 18, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/462,887*
FILING DATE: *April 15, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/11706*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

M. Sias

M. SIAS
Certifying Officer

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

04-16-03 #1/pro

JC648 U.S. PTO 04/15/03

Please type a plus sign (+) inside this box → [+]

PTO/SB/16 (8-00)
Approved for use through10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Richard D.	Shunnarah	c/o Metgen, Inc. PO Box 76411 Atlanta, Georgia 30358

☐ *Additional inventors are being named on the____ separately numbered sheets attached hereto*

JC648 U.S. PTO 60/462887 04/15/03

TITLE OF THE INVENTION (280 characters max)

MEDICAL DEVICE FOR MONITORING BLOOD PHENYLALANINE LEVELS

CORRESPONDENCE ADDRESS

Direct all correspondence to:

☒ Customer Number [ ] →

Place Customer Bar Code Label here 32361

PATENT TRADEMARK OFFICE

OR *Type Customer Number here*

☐ Firm or Individual Name					
Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages*	11	☐ CD(s), Number	
☐ Drawing(s) *Number of Sheets*		☒ Other (specify)	postcard receipt, Express Mail Cert.
☐ Application Data Sheet. See 37 CFR 1.76			

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

		FILING FEE AMOUNT ($)
☒ Applicant claims small entity status. See 37 CFR 1.27.		
☐ A check or money order is enclosed to cover the filing fees		
☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number	50-1561	$80.00
☐ Payment by credit card. Form PTO-2038 is attached.		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Eugene C. Rzucidlo

Date 04/15/03

REGISTRATION NO. *(if appropriate)* 31,900

Docket Number: 55142.010100

TYPED or PRINTED NAME Eugene C. Rzucidlo

TELEPHONE 212 801 2100

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C.

P19SMALL/REV05

MEDICAL DEVICE FOR MONITORING BLOOD PHENYLALANINE LEVELS

INVENTOR: RICHARD D. SHUNNARAH

Attorney Docket No. 55142.010100

MEDICAL DEVICE FOR MONITORING BLOOD PHENYLALANINE LEVELS

Field of The Invention

The present invention relates to a medical device for monitoring blood phenylalanine with respect to PKU management and treatment.

Background of The Invention

Phenylketonuria ("PKU") is a metabolic genetics disorder characterized by the inability of the body to utilize the essential amino acid, phenylalanine. Individuals with PKU accumulate too much phenylalanine, which is one of the amino acids found in protein-containing foods. For unknown reasons, an excess of phenylalanine in an infant's body is harmful to the development of the brain causing mental retardation unless treated during early infancy. When a very strict diet low in phenylalanine is initiated early and well maintained, individuals diagnosed with PKU can expect normal development and a normal life span. Treatment consists of lifelong dietary management and counseling, as well as continued blood phenylalanine monitoring.

PKU is caused by mutation in the gene that alters the function of the enzyme phenylalanine hydroxylase (PAH). This enzyme would normally convert phenylalanine to the amino acid tyrosine. In those individuals with PKU, the failure of the conversion results in a buildup of phenylalanine. Through a mechanism that is not well understood, the excessive amounts of phenylalanine is

toxic to the central nervous system and causes the severe problems associated with PKU. Damage to the brain causes marked mental retardation by the end of the first year of life. Older children may develop movement disorders. Symptoms can include skin rashes, hyperactivity, mental retardation, seizures, microcephaly, speech delays, tremors, behavior abnormalities, delayed mental and motor skills, an offensive odor to sweat an urine, light coloration (complexion, hair and eyes).

In those individuals diagnosed with PKU, each will have varying amounts of enzyme deficiency. Some individuals have enough enzyme activity that the diet can be extensive, while others may have a very strict diet. The healthcare professionals at a PKU treatment program must determine the nature of the diet for an individual diagnosed with PKU.

In 2000, the National Center for Health Statistics reported 4,058,814 births in the United States. At the incidence rate of 1:10,000 approximately 405 births were diagnosed with PKU in the United States in 2000. It is estimated that approximately 14,000 individuals as infants, adolescents and adults reside in the United Sates diagnosed with PKU.

PKU is a genetic inborn error of metabolism that is detectable during the first days of life with appropriate blood testing via newborn screening. Universal screening of newborn babies began in the United States approximately 40 years ago with the discovery of the cause of PKU and the blood test designed to detect

this metabolic genetics disorder. Dr. Robert Guthrie of the University of Buffalo developed the newborn screening test for PKU in 1961. Massachusetts became the first state to mandate screening for a genetic disorder in 1963. The Guthrie test for PKU is now mandated by all 50 states and the District of Columbia. Early screening, special diets and continued blood monitoring have allowed these children to grow normally and lead full and productive lives.

Most, if not all infants born with PKU will develop mental retardation without treatment. Treatment of those affected with PKU includes a strict diet regimen that is low in, or free of phenylalanine, particularly when the child is growing. To prevent mental retardation, treatment must begin in early infancy to ensure normal mental development. As a result of the problems associated with the discontinuation of the diet, it is believed that the diet, as well as the treatment regimen, should be maintained for life.

The treatment of PKU is complex, requiring routine collection of blood samples, maintenance of a highly restrictive diet, recording of food intake, and visits to a PKU treatment program. In the United States, each state screens the blood phenylalanine level of all newborns within the first days of life.

The goal of PKU treatment is to maintain a blood phenylalanine level between 2 and 10 mg/dL (120-600 micromol/L). Frequent monitoring of blood phenylalanine levels is of paramount importance, especially during the early years of life; with less frequent monitoring as age increases.

The frequency of blood phenylalanine monitoring will vary according to the individual's needs. *"Development of a reliable home-testing method is recommended, as well as measures to increase adherence."* (NIH Consensus Statement on Phenylketonuria: Screening and Management, October 2000)

There are numerous obstacles to overcome in the blood drawing necessary for the monitoring of phenylalanine levels in those individuals affected with PKU. Especially in children, blood drawing can be a hectic and frustrating experience for both the patient as well as the person involved with the blood draw. Preparing a child for a blood draw, gathering of needed materials including lancets, anesthetic creams, alcohol pads, Band-Aids, filter paper, address labels/envelopes for mailing, etc., is difficult at best. In addition, waiting times for test results can delay needed changes in treatment regimens. The constant needs and concerns for obtaining blood samples and sending the samples to a laboratory or the constant travel and difficulties inherent in those travels provides a unique need in a highly specialized marketplace for a medical device for monitoring blood phenylalanine.

It is an objective of the invention to provide a specialized blood monitoring product for use in metabolic genetic disorders. More specifically, it is an objective of the invention to provide a blood-monitoring product for measuring phenylalanine levels in those individuals affected with PKU who are under strict

medical supervision. A still further objective is to provide a blood phenylalanine monitoring product for in-home use by those individuals affected with PKU.

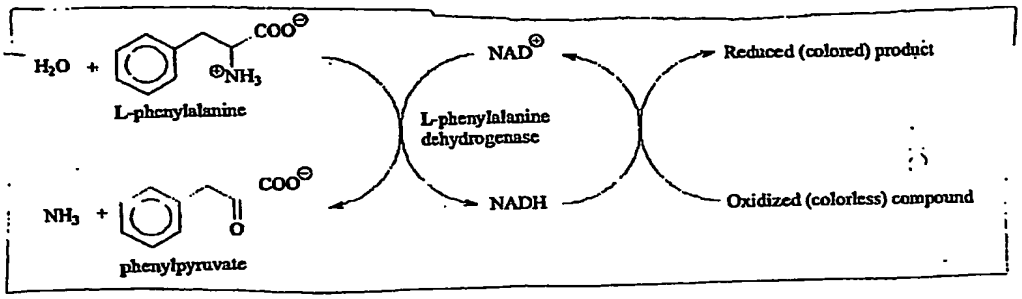
Summary of The Invention

The present invention relates to a medical device similar to a glucose monitor used by diabetics which enables individuals affected with PKU to routinely monitor blood phenylalanine levels at home on an as needed basis by the individual. The present device routinely monitors blood phenylalanine levels as necessitated by the PKU treatment regimen. In a preferred embodiment the present device will further comprise a memory storage of blood phenylalanine results over a lengthy treatment regimen. An embodiment of the device is such that blood sample drops can be placed on test strips that will continue to be purchased on an as needed basis as deemed appropriate by the prescribing genetics physician.

Detailed Description of the Invention

The present home monitor for blood phenylalanine makes use of the enzyme phenylalanine dehydrogenase. As illustrated below, this enzyme converts phenylalanine to phenylpyruvate, with the concomitant production an equivalent amount of NADH. A colorimetric assay will then be used for detection of the NADH. For example, as illustrated below, NADH reduces a colorless tetrazolium compound to a colored compound that can be seen visually or measured by colorimetry.

Oxidation of L-phenylalanine coupled to color formation



The NADH produced is measured colorimetrically using an election acceptor detection system.

The consensus 'acceptable' range for blood phenylalanine is 120 to 360 µmoles/L. In practice, the upper limit is usually raised after five years of age to 480 µmoles/L, and then is 'allowed' to go even higher after age ten if dietary compliance becomes an issue. There is also a need to monitor women during pregnancy.

The requisite limits of detection for a home monitor will be influenced by the sample volume available. The volume of blood from a finger stick is approximately 30µL. Assuming a 30µL drop of blood is used, the total amount of phenylalanine at the optimum lower limit of 120 µmoles/L is 0.60 µg, and at the optimum upper limit 360 µmoles/L is 1.8 µg. A lower limit of detection would need to be far enough below the 0.60 µg control value to accurately detect when the phenylalanine level is actually too low instead of just appearing to be low due to statistical variation between repeated measurements.

Several color reagents are useful and the limit of detection is influenced by the intensity of the color formed. Thionine, Rose Bengal, Methylene Blue, Azure C have been shown to react directly with NADH. Tetrazolium salts may also be used but may require an electron mediator such as 1-methoxy phenazine methosuflate.

In the last several decades analytical and clinical chemistry has developed to the point where many useful analytical measurements can be made using relatively simple and inexpensive instrumentation and often by unskilled personnel. Some of these technologies have now become over the counter, readily available, kits and instruments for home use. The most common of these is quantitative glucose measurement, used regularly by millions of Diabetics throughout the world. Using a microlancet to generate a small (50-100 microliter) blood droplet, the patient transfers the blood sample to a dip stick device, which serves to collect the sample, performs needed separation steps, and delivers the sample to one or more analytical zones in which a specific chemical reaction is carried out, resulting in a signal which is read by a small, inexpensive analytical instrument. In the case of diabetes, glucose specific dipsticks are used and small hand held reflectance colorimeters, commonly called Glucometers, are employed with acquisition costs in the range of $30 - 100 or more.

The individual Dipsticks cost in the range of 50 cents to $2.00, depending on the manufacturer and quantity considerations. In addition to the enzyme based

colorimetric assays used for glucose, immunoassays can also be employed, the most common of which is the over the counter pregnancy test. The current over the counter cholesterol test is an enzyme based colorimetric system.

The major Diabetes Control and Complications Trial (DCCT) recently documented the enhanced health benefits of tight glycemic control for diabetes. Regular monitoring of glucose and regulation of insulin intake leads to much more effective management of the disease and the minimization of the chronic complications which are so burdensome to both the patient and to the health care system.

The diabetes community is leading and driving major research and development activities to further improve the measurement and monitoring of glucose and of other metabolites important to diabetes, with an emphasis on sampling methods which do not involve the trauma and discomfort of blood sampling. There is a move towards the use of interstitial fluid as the analytical sample and even to the development of truly non-invasive methods of analysis. Considerable research and development is now being focused upon minimally invasive approaches for obtaining samples of interstitial fluids for glucose analysis. Such fluid can be collected from the skin epidermal layer, which is devoid of blood vessels or nerves. The process is therefore painless and bloodless.

The present invention utilizes the known technology for glucose testing adapted for QO PKU management, i.e., for phenylalanine blood level monitoring.

It is contemplated that the next generation will utilize painless and bloodless technology.

What is claimed.

1. A hand-held, battery operated medical device adapted for the monitoring of blood levels of phenylalanine utilizing colormetric analysis, comprising a unit containing testing elements, or insertion means for receiving a substiate having a test blood sample thereon and a means on said device for displaying a test result for a level of phenylalanine in the test sample.

2. The device of claim 1, further comprising a memory means for storing previous test sample results and means for displaying the stored test sample result.

3. The device of claim 2, possibly comprising a means to allow blood phenylalanine determinations to be downloaded to physicians offices.

4. A device used in the monitoring of blood phenylalanine levels wherein the device is non-invasive utilizing, for example, interstitial fluids.

ABSTRACT

A hand-held, battery operated medical device adapted for the monitoring of blood levels of phenylalanine utilizing colormetric analysis, comprising a unit containing testing elements, or insertion means for receiving a substiate having a test blood sample thereon and a means on said device for displaying a test result for a level of phenylalanine in the test sample.

June 18, 2004

PCT DIVISION
34 CHEIMIN DES COLUMBETTES
GENEVA, 1211
GENEVA, 20, SWITZERLAND

This is to inform you that the document requested in your order dated 06-16-2004 is a true reproduction of the official office record copy of that document:

09734628 CERTIFIED PCT APP AS FILED-MAIL 1

☐ The enclosed office document is a reproduction from the official office record copy and has been recorded using high quality scanning or microfilm equipment. Copies of page/papers that were not scannable have not been included, nor have pages/papers received after the original filing date. Copies of these pages/papers may be ordered separately.

☑ The enclosed document is a reproduction of the best available source of the official office record copy of that document.

If you have any questions or need additional information, please contact our Customer Service Department.

Mailing Address:
Mail Stop Document Services,
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Delivery Address:
U.S. Patent and Trademark Office
Office of Public Records, Customer Service
1213 Jefferson Davis Highway, Suite 300
Arlington VA 22202

Order your copies of USPTO documents on the Web. It's fast, easy, and secure! Go to (http://ebiz1.uspto.gov/oems25p/index.html) and order today!

Voice: (703) 308-9726 Fax: (703) 308-7048 E-Mail: mailto:DSD@USPTO.GOV

Ref:MS 1184092

This Page is inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- [X] BLACK BORDERS
- [X] IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- [X] FADED TEXT OR DRAWING
- [ ] BLURED OR ILLEGIBLE TEXT OR DRAWING
- [ ] SKEWED/SLANTED IMAGES
- [X] COLORED OR BLACK AND WHITE PHOTOGRAPHS
- [ ] GRAY SCALE DOCUMENTS
- [ ] LINES OR MARKS ON ORIGINAL DOCUMENT
- [ ] REPERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- [ ] OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning documents *will not* correct images problems checked, please do not report the problems to the IFW Image Problem Mailbox